DESCRIPTION

Adiponectin production enhancer

Technical field

The present invention relates to a pharmaceutical composition containing as an active ingredient one or more HMG-CoA reductase inhibitor(s) for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract, and coronary artery disease), hypertension, obesity or arteriosclerosis; and treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome, and

a method comprising administration of an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract, and coronary artery disease), hypertension, obesity or arteriosclerosis; and treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease),

hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome.

Background art

Adiponectin is a protein that is specifically produced and secreted from adipocytes, and is intimately involved in energy balance and glucose or lipid metabolism (Maeda, K. et al., Biochemical and Biophysical Research Communications, 1996, 221, 286-289). In actuality, in patients with circulatory diseases, diabetes, obesity, etc., blood adiponectin concentration decreases (Ouchi, N. et al., Circulation, 1999, 100, 2473-2476; Lindsay, R.S. et al., Lancet, 2002, 360, 57-58; Arita, Y. et al., Biochemical and Biophysical Research Communications, 1999, 257, 79-83). In addition, kidney disease patients exhibiting low blood adiponectin concentrations are known to have a higher mortality rate due to circulatory diseases than patients with high blood adiponectin concentrations (Zoccali, C. et al., Journal of American Society of Nephrology, 2002, 13, 134-141). Thus, disease states having decreased blood adiponectin concentrations, namely hypoadiponectinemia, are thought to be intimately related to lifestyle diseases such as circulatory diseases (arteriosclerosis, hypertension, etc.), diabetes or obesity, and are believed to be one of their basic causes (Weyer, C. et al., The Journal of Clinical Endocrinology & Metabolism, 2001, 86, 1930-1935; Hotta, K. et al., Diabetes, 2001, 50, 1126-1133). Thus, the treatment or prevention of hypoadiponectinemia is also useful in the treatment or prevention of the aforementioned lifestyle diseases caused by hypoadiponectinemia.

Adiponectin is known to have actions of suppressing adhesion of THP-1 cells to vascular endothelial cells, expression of adhesion molecules, differentiation of

vascular smooth muscle cells, macrophage foam cell formation, and the like (Ouchi, N. et al., Circulation, 1999, 100, 2473-2476; Ouchi, N. et al., Circulation 2001, 103, 1057-1063; Arita, Y. et al., Circulation 2002, 105, 2893-2898; Ouchi, N. et al., Circulation, 2000, 102, 1296-1301; Yokota, T. et al., Blood, 2000, 96, 1723-1732). These biological phenomena are intrinsic phenomena that occur during the initial stage of the onset of arteriosclerosis (Ross, R. et al., Nature, 1993, 362, 801-809), and the inhibitory effects demonstrated by adiponectin on these phenomena are extremely useful for the treatment or prevention of arteriosclerosis. In addition, increasing adiponectin concentration has been shown to have therapeutic effects on arteriosclerosis in an actual animal model (Okamoto, Y. et al., Circulation, 2002, 106, 2767-2770).

In addition, adiponectin is also intimately related to insulin resistance and diabetes (Kondo, H. et al., Diabetes, 2002, 51, 2325-2328). Insulin resistance is known to increase in the presence of hypoadiponectinemia (Weyer, C. et al., The Journal of Clinical Endocrinology & Metabolism, 2001, 86, 1930-1935; Hotta, K. et al., Diabetes, 2001, 50, 1126-1133), and in an animal model, administration of adiponectin is known to demonstrate glucose metabolism ameliorative action by having effects of improving insulin resistance, suppressing glucose production in the liver, and the like (Yamauchi, T., et al., Nature Medicine, 2001, 7, 941-946; Berg, A.H. et al., Nature Medicine, 2001, 7, 947-953; Combs, T.P. et al., Clinical Investigation, 2001, 108, 1875-1881). Thus, increasing blood adiponectin concentration is useful for the treatment or prevention of diabetes and diabetes complications caused thereby.

Diseases states that exhibit increased insulin resistance, namely insulin resistance syndrome, are considered to be a principal cause of diabetes as well as the fundamental cause of lifestyle diseases such as circulatory diseases (arteriosclerosis, hypertension, etc.) or obesity (McVeigh, G.E. et al., Current Diabetes Reports, 2003, 3, 87-92; Chaudhuri, A. et al., Current Diabetes Reports, 2002, 2, 305-310; Sorisky, A. et al., American Journal of Therapeutics, 2002, 9, 516-521), and improvement of insulin resistance plays an important role in the treatment or prevention of the aforementioned lifestyle diseases. In other words, improvement of insulin resistance is also useful for the treatment or prevention of the aforementioned lifestyle diseases caused by insulin resistance syndrome. As previously mentioned, since adiponectin has an action of improving insulin resistance (Yamauchi, T. et al., Nature Medicine, 2001, 7, 941-946), a medicament that enhances adiponectin production is useful for the treatment or prevention of insulin resistance syndrome, as well as the treatment or prevention of diabetes, diabetes complications, circulatory diseases (arteriosclerosis, hypertension, etc.) or obesity caused by insulin resistance syndrome.

In addition, the concepts of Syndrome X, metabolic syndrome, and the like have recently been advocated as disease states that increase the risk of coronary artery disease through a complex relationship with abnormal lipid metabolism diseases, diabetes, insulin resistance syndrome, and so forth (Reave, G.M., Diabetes, 1988, 37, 1595-1607; DeFronzo, R.A. et al., Diabetes Cara, 1991, 14, 173-194; Matsuzawa, Y., Nihon-Naikagaku-Zasshi (J. Jap. Soc. Internal Medicine), 1995, 84, 209-212). As previously described, since adiponectin is able to contribute to the

treatment or prevention of the respective causes of Syndrome X, metabolic syndrome, and the like a medicament that enhances the production of adiponectin is also useful for the treatment or prevention of Syndrome X, metabolic syndrome, and the like.

On the basis of the above, a medicament that enhances adiponectin production has an action of improving insulin resistance and is useful as a pharmaceutical composition for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract, and coronary artery disease), hypertension, obesity or arteriosclerosis; and treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome.

Although certain types of thiazolidine dione compounds or cannabinoid CB_1 receptor antagonists are known to demonstrate action of enhancing adiponectin production (for example, Maeda, N. et al., Diabetes, 2001, 50, 2094-2099; Bensaid, M. et al., Molecular Pharmacology, 2002, 360, 1623-1630; etc.), HMG-CoA reductase inhibitors have not been known to demonstrate adiponectin production enhancing action or therapeutic or preventive effects for hypoadiponectinemia.

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors are well-known hyperlipemia therapeutic medicaments (for example, US Patent No. 4346227, etc.). Statins are typical HMG-CoA reductase inhibitors, and

disease preventive effects in humans have been confirmed in various clinical studies. For example, pravastatin has been reported to demonstrate effects (preventive effects) of suppressing the onset of arteriosclerosis, coronary artery disease and diabetes in a clinical study targeted at hyperlipemia patients (for example, MacMahon, S. et al., Circulation, 1998, 97, 1784-1790; Shepherd, J. et al., Lancet, 2002, 360, 1623-1630; Freeman, D.J. et al., Circulation, 2001, 103, 357-362; etc.).

However, HMG-CoA reductase inhibitors are not known to demonstrate therapeutic effects for arteriosclerosis or diabetes, or therapeutic or preventive effects for diabetes complications, hypertension or obesity.

In addition, although certain types of HMG-CoA reductase inhibitors have been reported to have an action of improving insulin resistance (for example, Mangaloglu, L. et al., Metabolism, Clinical and Experimental, 2002, 51, 409-418; Cingozbay, B.Y. et al., Journal of International Medical Research, 2002, 30, 21-25; Paolisso, G. et al., Atherosclerosis, 2000, 150, 121-127; etc.), pravastatin and rosuvastatin have heretofore not been known to have an action of improving insulin resistance.

Disclosure of the invention

The inventors of the present invention found that an HMG-CoA reductase inhibitor has superior adiponectin production enhancing action, and is useful as a pharmaceutical composition for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract, and

coronary artery disease), hypertension, obesity or arteriosclerosis; and treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome, thereby leading to completion of the present invention.

The present invention provides a pharmaceutical composition containing as an active ingredient one or more HMG-CoA reductase inhibitor(s), for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract, and coronary artery disease), hypertension, obesity or arteriosclerosis; and treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome, and

a method comprising administration of an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract, and coronary artery disease), hypertension, obesity or arteriosclerosis; and treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy,

neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome.

The present invention is:

(1) a pharmaceutical composition for enhancement of adiponectin production comprising as an active ingredient one or more HMG-CoA reductase inhibitor(s);

(2) a pharmaceutical composition as (1), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin;

(3) a pharmaceutical composition as (1), wherein the HMG-CoA reductase inhibitor is a water-soluble HMG-CoA reductase inhibitor;

(4) a pharmaceutical composition as (1), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(5) a pharmaceutical composition as (1), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(6) a pharmaceutical composition as (1), wherein the HMG-CoA reductase inhibitor is pravastatin;

(7) a pharmaceutical composition for the treatment or prevention of hypoadiponectinemia comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(8) a pharmaceutical composition as (7), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(9) a pharmaceutical composition as (7), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(10) a pharmaceutical composition as (7), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

(11) a pharmaceutical composition for improving insulin resistance comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(12) a pharmaceutical composition as (11), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(13) a pharmaceutical composition as (11), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(14) a pharmaceutical composition as (11), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

(15) a pharmaceutical composition for the treatment or prevention of Syndrome X or metabolic syndrome comprising as an active ingredient one or more HMG-CoA reductase inhibitor(s);

(16) a pharmaceutical composition as (15), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin;

(17) a pharmaceutical composition as (15), wherein the HMG-CoA reductase inhibitor is a water-soluble HMG-CoA reductase inhibitor;

(18) a pharmaceutical composition as (15), wherein the HMG-

CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(19) a pharmaceutical composition as (15), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(20) a pharmaceutical composition as (15), wherein the HMG-CoA reductase inhibitor is pravastatin;

(21) a pharmaceutical composition for the treatment or prevention of hypertension comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(22) a pharmaceutical composition as (21), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(23) a pharmaceutical composition as (21), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(24) a pharmaceutical composition as (21), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

(25) a pharmaceutical composition for the treatment or prevention of obesity comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(26) a pharmaceutical composition as (25), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(27) a pharmaceutical composition as (25), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament

selected from the group consisting of pravastatin and rosuvastatin;

(28) a pharmaceutical composition as (25), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

(29) a pharmaceutical composition for the treatment of arteriosclerosis comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(30) a pharmaceutical composition as (29), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(31) a pharmaceutical composition as (29), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(32) a pharmaceutical composition as (29), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

(33) a pharmaceutical composition for the treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia, comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(34) a pharmaceutical composition as (33), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(35) a pharmaceutical composition as (33), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament

selected from the group consisting of pravastatin and rosuvastatin;

(36) a pharmaceutical composition as (33), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

(37) a pharmaceutical composition for the treatment or prevention of hypertension, obesity or arteriosclerosis caused by insulin resistance syndrome, comprising as an active ingredient one or more water-soluble HMG-CoA reductase inhibitor(s);

(38) a pharmaceutical composition as (37), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(39) a pharmaceutical composition as (37), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(40) a pharmaceutical composition as (37), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin;

(41) a method for enhancement of adiponectin production comprising administration of an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(42) a method for treatment or prevention of Syndrome X or metabolic syndrome comprising administration of an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(43) a method as (41) or (42), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin;

(44) a method as (41) or (42), wherein the HMG-CoA reductase inhibitor is a water-soluble HMG-CoA reductase inhibitor;

(45) a method as (41) or (42), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin or a derivative thereof and rosuvastatin or a derivative thereof;

(46) a method as (41) or (42), wherein the HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(47) a method as (41) or (42), wherein the HMG-CoA reductase inhibitor is pravastatin;

(48) a method for treatment or prevention of hypoadiponectinemia comprising administration of an effective amount of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(49) a method for improving insulin resistance comprising administration of an effective amount of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(50) a method for treatment or prevention of hypertension comprising administration of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(51) a method for treatment or prevention of obesity comprising administration of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(52) a method for treatment of arteriosclerosis comprising administration of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(53) a method for treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by

hypoadiponectinemia comprising administration of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(54) a method for treatment or prevention of hypertension, obesity or arteriosclerosis caused by insulin resistance syndrome comprising administration of one or more water-soluble HMG-CoA reductase inhibitor(s) to a warm-blooded animal;

(55) a method as any one of (48) to (54), wherein the water-soluble HMG-CoA reductase inhibitor is a medicament selected from the group consisting of pravastatin and rosuvastatin;

(56) a method as any one of (48) to (54), wherein the water-soluble HMG-CoA reductase inhibitor is pravastatin; and,

(57) a method as any one of (41) to (56), wherein the warm-blooded animal is a human.

There are no particular restrictions on the HMG-CoA reductase inhibitor(s) serving as an active ingredient compound of the present invention provided it is a compound that demonstrates HMG-CoA reductase inhibitory action, examples of which include compounds having HMG-CoA reductase inhibitory action, pharmacologically acceptable salts thereof, or pharmacologically acceptable esters thereof as described in Japanese Patent Application (Kokai) No. Sho 57-2240 (US Patent No. 4346227), Japanese Patent Application (Kokai) No. Sho 57-163374 (US Patent No. 4231938), Japanese Patent Application (Kokai) No. Sho 56-122375 (US Patent No. 4444784), Japanese Patent Application (Kokai) No. Sho 60-500015 (US Patent No. 4739073), Japanese Patent Application (Kokai) No. Hei 1-216974 (US Patent No. 5006530), Japanese Patent Application (Kokai) No. Hei 3-58967 (US Patent No. 5273995), Japanese Patent Application

(Kokai) No. Hei 1-279866 (US Patent Nos. 5854259 and 5856336) or Japanese Patent Application (Kokai) No. Hei 5-178841 (US Patent No. 5260440), preferably pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin or rosuvastatin, more preferably pravastatin or rosuvastatin, and most preferably pravastatin.

For an HMG-CoA reductase inhibitor serving as an active ingredient compound of the present invention, a water-soluble HMG-CoA reductase inhibitor such as pravastatin and rosuvastatin is preferable. In the present invention, a water-soluble HMG-CoA reductase inhibitor is an HMG-CoA reductase inhibitor in which the logarithm of the partition coefficient measured between phosphate buffer solution (pH 7.0 to 8.0, preferably pH 7.0 to 7.5, and more preferably pH 7.0) and 1-octanol [log(test substance concentration in 1-octanol phase/test substance concentration in buffer solution phase)] is 1.0 or less (preferably 0.5 or less, and more preferably 0.0 or less) (McTaggart, F. et al., The American Journal of Cardiology, 2001, 87, 28B-32B; Chapman, M. J. et al., Atherosclerosis Supplements, 2002, 33-37; Shimada, Y. et al., Progress in Medicine, 1998, 18, 957-962). The aforementioned partition coefficient can be measured according to ordinary methods (Partition Coefficient (n-octanol/water), OECD Guidelines for Testing of Chemicals, Section 1, Physical Chemical Properties, Paris, 1981, 107; Shimada, Y. et al., Progress in Medicine, 1998, 18, 957-962) or similar methods thereto.

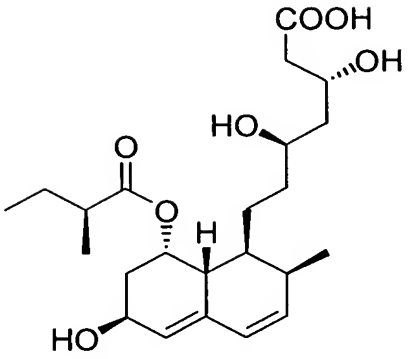
In addition, for an HMG-CoA reductase inhibitor serving as an active ingredient compound of the present invention, pravastatin or derivative thereof, or rosuvastatin or derivative thereof, is preferable. In the present invention, a derivative of pravastatin is a

compound having HMG-CoA reductase inhibitory action, a pharmacologically acceptable salt thereof or ester thereof as described in Japanese Patent Application (Kokai) No. Sho 57-2240 (US Patent No. 4346227), while a derivative of rosuvastatin is a compound having HMG-CoA reductase inhibitory action, a pharmacologically acceptable salt thereof or ester thereof as described in Japanese Patent Application (Kokai) No. Hei 5-178841 (US Patent No. 5260440).

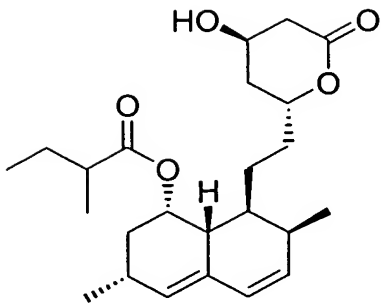
Pravastatin is (+)-(3R,5R)-3,5-dihydroxy-7-[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-[(S)-2-methylbutyryloxy]-1,2,6,7,8,8a-hexahydro-1-naphthyl]heptanoic acid, and includes its pharmacologically acceptable salts or esters (for example, monosodium salt of the aforementioned pravastatin, etc.) as described in Japanese Patent Application (Kokai) No. Sho 57-2240 (US Patent No. 4346227). Lovastatin is (+)-(1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl (S)-2-methylbutyrate, and includes its pharmacologically acceptable salts or esters as described in Japanese Patent Application (Kokai) No. Sho 57-163374 (US Patent No. 4231938). Simvastatin is (+)-(1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl 2,2-dimethylbutyrate, and includes its pharmacologically acceptable salts or esters as described in Japanese Patent Application (Kokai) No. Sho 56-122375 (US Patent No. 4444784). Fluvastatin is (±)-(3R*,5S*,6E)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, and includes its pharmacologically acceptable salts or esters (for example, monosodium salt of the aforementioned fluvastatin, etc.) as

described in Japanese Patent Application (Kokai) No. Sho 60-500015 (US Patent No. 4739073). Cerivastatin is (3R,5S,6E)-7-[4-(4-fluorophenyl)-2,6-di-(1-methylethyl)-5-methoxymethylpyridin-3-yl]-3,5-dihydroxy-6-heptenoic acid, and includes its pharmacologically acceptable salts or esters (for example, monosodium salt of the aforementioned cerivastatin, etc.) as described in Japanese Patent Application (Kokai) No. Hei 1-216974 (US Patent No. 5006530). Atorvastatin is (3R,5S)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-phenylaminocarbonyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, and includes its pharmacologically acceptable salts or esters (for example, 1/2 calcium salt of the aforementioned atorvastatin, etc.) as described in Japanese Patent Application (Kokai) No. Hei 3-58967 (US Patent No. 5273995). Pitavastatin is (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]-6-heptenoic acid, and includes its pharmacologically acceptable salts or esters (for example, 1/2 calcium salt of the aforementioned pitavastatin, etc.) as described in Japanese Patent Application (Kokai) No. Hei 1-279866 (US Patent Nos. 5854259 and 5856336). Rosuvastatin is (+)-(3R,5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid, and includes its pharmacologically acceptable salts or esters (for example, 1/2 calcium salt of the aforementioned rosuvastatin, etc.) as described in Japanese Patent Application (Kokai) No. Hei 5-178841 (US Patent No. 5260440).

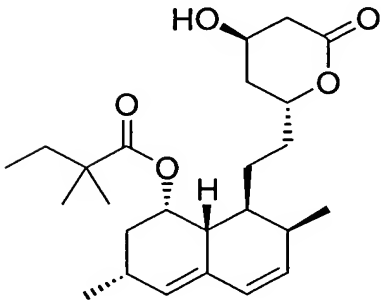
The following indicates the two-dimensional structural formulas of major HMG-CoA reductase inhibitors.



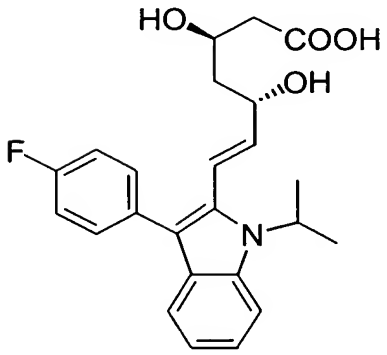
Pravastatin



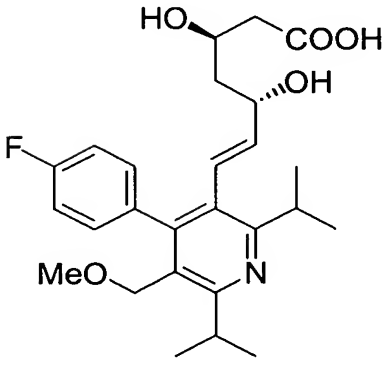
Lovastatin



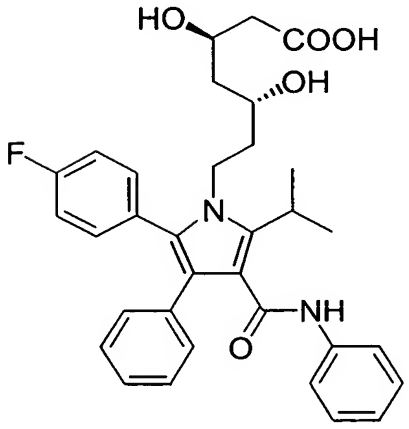
Simvastatin



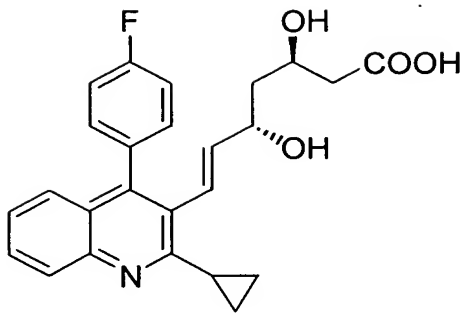
Fluvastatin



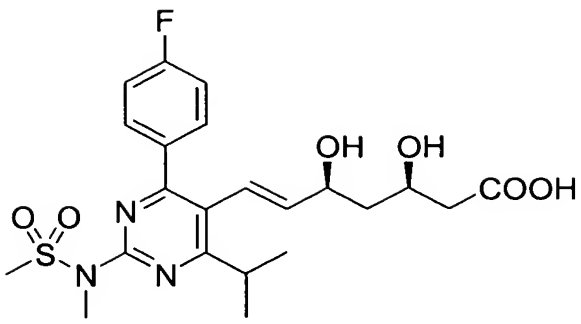
Cerivastatin



Atorvastatin



Pitavastatin



Rosuvastatin

In the case where the aforementioned HMG-CoA reductase inhibitor has an asymmetric carbon, all of its racemate, its optical isomers and mixtures thereof are included in the HMG-CoA reductase inhibitor of the present invention. In addition, hydrates of the aforementioned HMG-CoA reductase inhibitors are also included in the HMG-CoA reductase inhibitor of the present invention.

For an HMG-CoA reductase inhibitor serving as an active ingredient compound in the present invention, one type of compound can be used alone, or a mixture of two or more types of compounds can be used. In the case of using a mixture of two or more types of compounds, the compounds can be used simultaneously or each of compounds can be used separately at different times.

An HMG-CoA reductase inhibitor serving as an active ingredient of the present invention can easily be prepared in accordance with known methods [for example, Japanese Patent Application (Kokai) No. Sho 57-2240 (US Patent No. 4346227), Japanese Patent Application (Kokai) No. Sho 57-163374 (US Patent No. 4231938), Japanese Patent Application (Kokai) No. Sho 56-122375 (US Patent No. 4444784), Japanese Patent Application (Kokai) No. Sho 60-500015 (US Patent No. 4739073), Japanese Patent Application (Kokai) No. Hei 1-216974 (US Patent No. 5006530), Japanese Patent Application

(Kokai) No. Hei 3-58967 (US Patent No. 5273995), Japanese Patent Application (Kokai) No. Hei 1-279866 (US Patent Nos. 5854259 and 5856336), Japanese Patent Application (Kokai) No. Hei 5-178841 (US Patent No. 5260440), etc.] or similar methods thereto.

Industrial applicability

In the case of using the HMG-CoA reductase inhibitor(s) serving as an active ingredient of the present invention as a pharmaceutical (pharmaceutical composition for treatment or prevention of the aforementioned diseases), it can be administered in the form of a bulk medicament of the pharmaceutical itself; or it can be orally administered in a formulation such as tablet, capsule, granules, pill, powder, liquid, syrup, troche, suspension, emulsion, etc. or be parenterally administered in a formulation such as an injection, suppository or patch, etc., which formulations are made by mixing the HMG-CoA reductase inhibitor with a suitably pharmacologically acceptable excipient, binder and so forth. An oral administration is preferred.

These formulations are prepared using well-known methods using additives such as excipients, binders, disintegrants, lubricants, emulsifiers, stabilizers, corrigents, diluents, injection solvents and so forth.

An excipient may be, for example, an organic excipient or inorganic excipient. Examples of organic excipients include sugar derivatives such as lactose, sucrose, glucose, mannitol and sorbitol; starch derivatives such as cornstarch, potato starch, alpha starch, dextrin and carboxymethyl starch; cellulose derivatives such as crystalline cellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, calcium carboxymethyl

cellulose, and internally-crosslinked sodium carboxymethyl cellulose; gum arabic; dextran; and, pullulan. Examples of inorganic excipients include silicic acid salt derivatives such as light anhydrous silicic acid, synthetic aluminum silicate, calcium silicate, and magnesium metasilicate aluminate; phosphoric acid salts such as calcium phosphate; carbonic acid salts such as calcium carbonate; and sulfuric acid salts such as calcium sulfate.

Examples of binders include the compounds as described for the aforementioned excipient; gelatin; polyvinylpyrrolidone; and, polyethylene glycol.

Examples of disintegrants include the compounds as described for the aforementioned excipient; chemically modified starch or cellulose derivatives such as crosscarmelose sodium and sodium carboxymethyl starch; and, crosslinked polyvinylpyrrolidone.

Examples of lubricants include talc; stearic acid; metal stearates such as calcium stearate and magnesium stearate; colloidal silica; waxes such as bee gum and spermaceti; boric acid; glycol; DL-leucine; carboxylic acids such as fumaric acid and adipic acid; carboxylic acid sodium salts such as sodium benzoate; sulfates such as sodium sulfate; lauryl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; silicic acids such as anhydrous silicic acid and silicic acid hydrate; and the above starch derivatives as for the aforementioned excipients.

Examples of emulsifiers include colloidal clays such as bentonite and bee gum; metal hydroxides such as magnesium hydroxide and aluminium hydroxide; anionic surfactants such as sodium lauryl sulfate and calcium stearate; cationic surfactants such as benzalkonium chloride; and, nonionic surfactants such as polyoxyethylene

alkyl ether, polyoxyethylene sorbitan fatty acid ester, and sucrose fatty acid ester.

Examples of stabilizers include parahydroxybenzoic acid esters such as methyl paraben and propyl paraben; alcohols such as chlorobutanol, benzyl alcohol and phenylethyl alcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid.

Examples of corrigents include ordinarily used sweeteners, sour flavourings, fragrances, etc..

Examples of diluents include water, ethanol, propylene glycol, ethoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid ester.

Examples of injection solvents include water, ethanol and glycerin.

The HMG-CoA reductase inhibitor(s) serving as an active ingredient of the present invention can be administered to a warm-blooded animal (and particularly a human). The dose can be varied depending on various conditions such as the symptoms and age of the patient. In the case of oral administration, 0.1 mg (preferably 0.5 mg) as a lower limit and 1000 mg (preferably 500 mg) as an upper limit can be administered once to six times per day for a human adult depending on the symptoms. In the case of parenteral administration, 0.01 mg (preferably 0.05 mg) as a lower limit and 100 mg (preferably 50 mg) as an upper limit can be administered once to six times per day for a human adult depending on the symptoms.

Since the HMG-CoA reductase inhibitor(s) serving as an active ingredient of the present invention has superior adiponectin production enhancing action, it is useful as a pharmaceutical composition for the treatment or prevention of diseases wherein blood adiponectin concentration

decreases due to the occurrence of that disease, and diseases that occur due to a decrease in blood adiponectin concentration (and preferably diseases wherein blood adiponectin concentration decreases due to the occurrence of that disease).

The HMG-CoA reductase inhibitor(s) serving as an active ingredient of the present invention is useful as a pharmaceutical composition for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis; and, treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome,

preferably for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; and treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome,

more preferably for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; and treatment or prevention of diabetes or arteriosclerosis caused by hypoadiponectinemia,

and even more preferably for enhancement of adiponectin production and treatment or prevention of hypoadiponectinemia.

In addition, the aforementioned pharmaceutical composition is preferably for warm-blooded animals, and more preferably for humans. A pharmaceutical composition for treatment or prevention of the present invention is preferably a pharmaceutical composition for treatment.

Best mode for carrying out the invention

The following provides a more detailed explanation of the present invention by indicating Examples and Formulation examples, but the present invention is not limited thereto.

(Example 1) Adiponectin production enhancing action (in vitro)

(1) Cell culturing

Preadipocyte cell line 3T3-L1 was purchased from the American Type Culture Collection (ATCC). The 3T3-L1 cells were plated onto a 24-well, collagen-coated plate and cultured to saturation in growth medium (DMEM, 25 mM glucose, 10% FCS, 100 u/ml penicillin, 0.1 mg/ml streptomycin) under conditions of 37°C and 5% CO_2. Five days after cell proliferation had reached a saturated state, the medium was replaced with medium (DMEM, 25 mM glucose, 10% FCS, 100 u/ml penicillin, 0.1 mg/ml streptomycin) to which had been added 1 μM insulin, 0.5 mM 3-isobutyl-1-methylxanthine and 1 μM dexamethazone to initiate adipocyte differentiation. Two days later, the medium was replaced with growth medium containing 1 μM insulin followed by additionally culturing the cells for 2 days. Subsequently, the medium was replaced with fresh growth medium every 3 days, and the 3T3-L1 adipocytes were prepared on day 10 after the start of differentiation.

Test compounds that were poorly soluble in water were used after dissolving in DMSO. Test compounds that were easily soluble in water were dissolved in sterile water followed by addition of the same amount of DMSO as that used for the aforementioned poorly water-soluble test compounds. In addition, in the case of test compounds that are poorly soluble in water, the test compound may be dissolved in ethanol and used following the addition of 0.1 N aqueous sodium hydroxide solution after shaking as necessary.

After allowing the 3T3-L1 cells to adequately differentiate into adipocytes, a test compound was added to the medium to a final concentration of 10 μM followed by culturing the cells for 48 hours. The cells were additionally cultured for 24 hours after replacing the medium. Following culturing, the cells were used for measurement of adiponectin mRNA, while the supernatant used for measurement of the amount of adiponectin secreted.

(2) Measurement of adiponectin mRNA

RNA was extracted from cells that had been treated with a test compound using Sepasol (Nacalai-Tesque). cDNA was then synthesized using the ThermoScript Reverse Transcriptase Kit (registered trade mark: Invitrogen) by using the extracted RNA as a template. The synthesized cDNA was amplified using FastStrand DNA Master SYBR Green I (Roche Diagnostics), and the amplified PCR product was detected with LightCycler (Roche Diagnostics). The sequences and SEQ ID numbers in the sequence listing to be described later for the primers used and the 36B4 used as an internal control are shown below.

Adiponectin: 5'-GATGGCAGAGATGGCACTCC-3'
(SEQ ID NO. 1: adiponectin PCR primer)
5'-CTTGCCAGTGCTGCGGTCAT-3'
(SEQ ID NO. 2: adiponectin PCR primer)

36B4: 5'-GCTCCAAGCAGATGCAGCA-3'
(SEQ ID NO. 3: 36B4 PCR primer)
5'-CCGGATGTGAGGCAGCAG-3'
(SEQ ID NO. 4: 36B4 PCR primer)

The adiponectin mRNA amount was measured according to quantitative RT-PCR. The amounts of adiponectin mRNA in the groups in which pravastatin and rosuvastatin were used as test compounds were 1.6 times and 1.3 times higher, respectively, than those in the control group.

(3) Measurement of amount of secreted adiponectin

Secretion of adiponectin into culture supernatant was detected by Western blotting. 0.5 μl of recovered culture supernatant were fractionated by 12.5% SDS-polyacrylamide gel electrophoresis, and the protein following fractionation was transferred to a PVDF membrane (Millipore). Subsequently, anti-adiponectin antibody was bound to the PVDF membrane and after washing with PBS, was reacted with antibody conjugated with Horseradish peroxidase. After washing the PVDF membrane, the adiponectin bands were detected using ECL Detection Reagents (Amersham-Pharmacia). The bands were quantified with a densitometer (Molecular Devices).

The amounts of secreted adiponectin were analyzed by Western blotting. The amounts of secreted adiponectin in the groups in which pravastatin and rosuvastatin were used as test compounds were 1.7 times and 1.6 times higher, respectively, than those in the control group.

On the basis of the results described in (2) and (3) above, an HMG-CoA reductase inhibitor serving as an active

ingredient of the present invention was determined to have superior action of enhancing the production of adiponectin, and to be useful as a pharmaceutical composition for enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome; etc..

(Example 2) Adiponectin production enhancing action (in vivo) and glucose uptake enhancing action

(1) Administration of Pravastatin to mice in feed

(i) Test animals

C57BL/6J mice (male, age 5 weeks) were purchased from Clea Japan, and used in the test after acclimating to the test environment for 1 week. The mice were housed 5 animals to a cage and given unrestricted access to feed (F2, Funabashi farm) and water.

(ii) Schedule

The body weights of the animals were measured and blood samples were collected on the day the test started, and the animals were divided into two groups of 5 animals per cage based on their body weights and blood glucose levels. Blood samples were collected at the start of the test and in weeks 6, 11 and 15 after the start of the test. Blood samples were collected from the tail vein in an amount equal to one heparinized capillary tube.

(iii) Administration method

Pravastatin powder was added to the F2 powder to 0.06% (wt/wt), uniformly mixed and provided to the animals in

individual cages. The amount of feed and general behaviour were checked at least once a day.

(iv) Measurement

Blood glucose levels were measured on the days when blood samples were collected. Adiponectin levels were measured simultaneously for all blood samples following completion of administration. The Glucose CII-Test Wako (Wako) and Mouse/Rat Adiponectin ELISA Kit (Otsuka Pharmaceutical) were respectively used for measurement.

(2) Insulin tolerance test using Pravastatin-dosed mice

A group administered with pravastatin by mixing in feed for 15 weeks and a non-dosed group of C57BL/6J mice (n=5) were fasted for 2 hours. After measuring the body weight of each animal, insulin (Humalin, Lilly) was administered intraperitoneally at 0.5 u/kg, and blood samples were collected from the tail vein immediately before the start of administration and at 15, 30, 60 and 90 minutes after the start of administration followed by measurement of blood glucose levels.

(3) Glucose uptake test using isolated adipocytes from Pravastatin-dosed mice

(i) Epididymal adipose tissue was excised from a group administered with pravastatin for 16 weeks and a non-dosed group of C57BL/6J mice (n=5). The excised adipose tissue was handled under conditions of 37°C at all times. The adipose tissue was cut into small pieces with a scissors, followed by the addition of medium (DMEM, 1 mM sodium pyruvate, 25 mM HEPES pH 7.4, 0.1% BSA, 100 u/ml penicillin, 0.1 mg/ml streptomycin) containing 1 mg/ml of collagenase I (Worshington), and shaking at 37°C and 80 rpm. Following the reaction, 2.5 volumes of the aforementioned medium were added, the adipocytes were screened out by passing the cell

suspension through a 260 μm mesh sieve, and again passed through a 100 μm mesh sieve to prepare an adipocyte suspension.

(ii) The glucose uptake test was carried out in the manner as described below. 100 μl of the aforementioned cell suspension, 90 μl of medium and 10 μl of insulin solution were added to a polystyrene tube, while stirring gently to uniformly distribute the adipocytes in each tube, and the adipocytes cultured for 30 minutes at 30°C. Subsequently, 0.6 μCi of ^{3}H-labeled 2-deoxyglucose was added and allowed to react for 30 minutes. Following the reaction, the cell suspension was immediately transferred to a centrifuge tube containing silicone oil and centrifuged. After cutting out the oil layer of the upper layer containing adipocytes with a knife, it was transferred to a glass vial containing 4 ml of Hionic Fluor (Perkin-Elmer) liquid scintillation counter cocktail followed by measurement of specific radioactivity. The amount of measured radioactivity of the ^{3}H-2-deoxyglucose was used as an indicator of the amount of glucose taken up by the cells.

(4) Results

In (1) above, pravastatin was administered to C57BL/6J mice for 15 weeks followed by measurement of blood glucose levels and adiponectin concentrations. Adiponectin concentrations were measured in the same manner as Example 1. Although there were no significant differences in blood glucose levels between the pravastatin dose group and non-dose group, adiponectin concentrations in the dose group were 1.28 times higher than in the non-dose group.

In the insulin tolerance test described in (2) above, the pravastatin dose group demonstrated significantly lower blood glucose levels than the non-dose group at 60 minutes

after administration of insulin (non-dose group blood glucose level: 148 mg/dl, dose group blood glucose level: 110 mg/dl).

In the C57BL/6J mouse adipocytes in (3) above, the pravastatin dose group demonstrated increased insulin sensitivity and increased glucose uptake more than the non-dose group. The amount of glucose uptake by the pravastatin dose group was 1.4 times greater than that by the non-dose group.

From the aforementioned results, an HMG-CoA reductase inhibitor serving as an active ingredient of the present invention was found to enhance adiponectin production, to increase insulin sensitivity and to enhance insulin-induced glucose uptake, and was determined to be useful as a pharmaceutical composition for the enhancement of adiponectin production; treatment or prevention of hypoadiponectinemia; improvement of insulin resistance; treatment or prevention of Syndrome X or metabolic syndrome; treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis; and the treatment or prevention of diabetes, diabetes complications (including retinopathy, nephropathy, neuropathy, cataract and coronary artery disease), hypertension, obesity or arteriosclerosis caused by hypoadiponectinemia or insulin resistance syndrome.

(Formulation Example 1) Tablets

After mixing 10 parts of pravastatin sodium, 71.55 parts of lactose, 20 parts of low substituted hydroxypropyl cellulose (LH21, Shin-Etsu Chemical), 20 parts of crystalline cellulose (Avicel PH101, Asahi Kasei) and 6.5

parts of magnesium metasilicate aluminate (Neusilin FL2, Fuji Chemical Industry) with a Henschel mixer (Mitsui Mining), 13 parts of a 10% aqueous solution of hydroxypropyl cellulose (Nippon Soda) and a suitable amount of water were added to the resulting mixture followed by kneading with a Henschel mixer. The resulting kneaded product was dried for 1 hour at 60°C with an air dryer. The resulting dried product was sized with a power mill (Dalton) equipped with a 1 mm ϕ diameter screen, and 129.35 parts of the resulting granules and 0.65 parts of magnesium stearate (NOF Corporation) were mixed with a V-mixer (Tokuju Seisakusho). The resulting mixture was formed into tablets to produce tablets having a diameter of 7.0 mm.